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ABSTRACT

This report describes research programs focusing on the sudden infant death syndrome (SIDS) and indicates some presently available results. Specific attention is given to research on sleep apnea, respiratory control, and hypoxia, as well as to infectious disease processes and immunology. Findings of a large-scale multidisciplinary SIDS project are discussed. In addition, various related research studies conducted by different agencies are described. Funds allocated to and estimated for public health service agencies are specified for the years 1980 through 1984. (RH)

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Special Report to Congress:

SUDDEN INFANT DEATH SYNDROME

FY 1983

National Institute of Child Health and Human Development

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

SUDDEN INFANT DEATH SYNDROME

The sudden infant death syndrome (SIDS) is defined as the sudden death of any infant or young child that is unexpected by history and where the death remains inexplicable after performance of an adequate postmortem examination. Also referred to as crib death, sudden unexplained death, and sudden death in infancy, this syndrome is a worldwide public health problem. In the United States, it is the leading cause of death between the ages of one and twelve months. Its incidence rate is estimated at 2 per 1,000 live births, accounting for the deaths of between 6,000 and 7,000 infants each year. The majority of these babies are between the ages of one and six months when they die suddenly, quietly, and unexpectedly during what is considered a normal sleep period.

The National Institute of Child Health and Human Development of the National Institutes of Health has primary Federal responsibility for research on the sudden infant death syndrome. Other Institutes supporting projects pertinent to SIDS include the National Institute of Neurological and Communicative Disorders and Stroke, and the National Heart, Lung, and Blood Institute. The Office for Maternal and Child Health, Bureau of Community Health Services, Health Services Administration has primary responsibility for counseling and information activities.

The NICHD's portfolio in SIDS encompasses research grants probing many facets of the problem: sleep state; respiratory functions in young infants at risk for SIDS and in the normally developing infant; the role of infection and immunological development; interactions of possible genetic factors and environmental influences; and autopsy findings regarding anatomical, histological and/or biochemical characteristics in SIDS victims.

A composite picture is evolving identifying special characteristics of the SIDS victim and the SIDS family. The analysis of the differences between intrauterine and extrauterine environments of infants who died of SIDS compared to normal living infants, and of those who died of other identifiable causes has expanded our base of knowledge and may facilitate identification of signs leading to death. Epidemiological data have highlighted risk factors for SIDS such as prematurity, low birth weight, postnatal growth retardation, chronic hypoxemia (decreased oxygen in the blood), and breathing difficulties; maternal factors include age less than 20 years, smoking during pregnancy, and not receiving prenatal care. A better understanding of the biology of maternal factors governing normal and abnormal fetal and neonatal growth and development will simultaneously facilitate the development of preventive approaches to SIDS. For example, prevention of prematurity might at the same time reduce the

number of SIDS victims. The concept that some conditions associated with high-risk pregnancy and high-risk infancy are contributing factors to the occurrence of the sudden infant death syndrome has been accepted by the scientific community. Events taking place in the intrauterine environment or in the early weeks of extrauterine life may modify the normal progression of maturational processes in the fetus and newborn. Although the infant may appear normal at birth, the ability to coordinate vital functions with sleep and feeding may be jeopardized so that minor stressful situations such as upper respiratory infections, sleep deprivation, etc., may precipitate a severe apnea episode and/or death.

Sleep Apnea, Respiratory Control, and Hypoxia

Research is examining the role of sleep apnea (cessation of respiration for a period of ten seconds or longer and spontaneous recovery noted during sleep) as an antecedent to death. Earlier studies suggested that some SIDS victims had suffered hypoxia for varying periods of time before death and this stimulated the research into apnea and respiratory control. To clarify this question, studies are delineating the development of the respiratory control center, the profile of ventilatory responses to carbon dioxide, and the operating respiratory controls during sleep. Any one abnormality may contribute to or can result in hypoxemia and/or a diminution of oxygen reaching the tissues of the body (hypoxia).

Studies carried out between 1973 and 1978, supported by two NICHD contracts with the University of Southern California and the University of California, Los Angeles obtained developmental physiologic data from 25 normal infants and 25 siblings of SIDS victims. Twelve-hour all-night sleep recordings were obtained at 1 week and at 1,2,3,4, and 6 months of age. These data were gathered under well-defined conditions, and their availability in computer compatible form allows physicians to evaluate and test of specific hypotheses. During FY 82, grantee, Dr. Ronald M. Harper and his team at the University of California, Los Angeles, continued work on the research hypothesis that the organization of sleep is disturbed in infants at risk for SIDS, and that they exhibit difficulty in "arousing" from sleep during circumstances which compromise their survival. Initially they described normative developmental curves for maturation of sleep states in addition to respiratory and motility parameters. Recent studies have documented developmental trends of the hourly periodic organization in EEG (electroencephalographic) activity in normal infants and described developmental curves for variables which are major contributors to the definition of sleep state. These studies were extended into a larger group of physiological variables, and have included cardiac, respiratory and motility parameters in measures of hourly periodic organization. The investigators concluded that the organization of sleep states is disturbed in infants at risk for SIDS and suggest that this disturbance results in a "failure to arouse" from normal stimulation during sleep or a difficulty in state transition. In

addition, these studies demonstrated that infants at risk showed an acceleration of EEG patterns in specific EEG bands. Such EEG development points to an alteration in a main component of state organization and will be useful in evaluating the "failure to arouse" hypothesis for SIDS.

Sleep state respiratory control is being studied in kittens by Dr. Dennis J. McGinty at the University of California at Los Angeles. Following initial studies under the NICHD contract referenced previously, Dr. McGinty is examining the brain mechanisms which mediate both normal and abnormal depression of breathing during sleep as a potential element of risk for SIDS. In earlier studies, he found that a practical method for co-activation of neurons of the reticular formation and breathing during sleep is vestibular stimulation produced by a rocking bed. Indeed, in kittens, it was determined that rocking is an effective stimulus to breathing during sleep, producing a facilitation of diaphragmatic electromyographic activity in both rapid-eye-movement (REM) and non-rapid-eye-movement sleep. This research permits the evaluation of a simple and practical tool for assisting infants at risk for SIDS.

Grantee, Dr. Bradley T. Thach and his team at Washington University, St. Louis, are performing studies of airway patency regulation in an animal model. Many infants at high risk for apnea present some degree of airway obstruction. In anesthetized rabbits, the investigators have determined that the airway pressure reflexes respond to changes of pressure and protect the airway from collapse from negative pressure. The changes in pressure are sensed through nerve endings superficially located in the nose and pharynx. Indeed, the investigators showed that when sensation provided by these nerve endings is obliterated, the animal is unable to use his upper airway and dies of asphyxia. These reflexes appear to be essential for spontaneous ventilation in the rabbit. In human infants who suffer apneic spells, these researchers found that a state of behavioral arousal characterized by gross motor activity and squirming movements is associated with with a markedly disordered respiratory pattern. This pattern seems to be a significant component of obstructive apnea. During FY 1982, these investigators began studies in infants at high risk for SIDS (e.g., had near-miss episode and/or have a positive family history). They demonstrated that in episodes of mixed apneas the initial event was the airway obstruction. Therefore research efforts are concentrating on this particular aspect.

Dr. Gabriel G. Haddad at Columbia University College of Physicians and Surgeons is continuing to study the changes of ventilatory and cardiovascular responses to hypoxia during sleep and wakefulness in growing puppies. Specific techniques have been developed to examine the mediation of hypoxic responses by adrenal hormones known as catecholamines during REM and quiet sleep. An important initial finding is that newborns have much higher levels of these hormones and brisker responses to hypoxia than adults.

Dr. Haddad and his team are examining the role of endorphins (chemicals in the brain whose effects on cells resemble those of opiates such as morphine) in the maturation of ventilatory and cardiovascular functions during sleep and wakefulness under normal and hypoxic conditions. Techniques were successfully developed to measure ventilation and record EEG and ECG with an experimental animal trained to remain in a specific chamber where oxygen and carbon dioxide concentration may be changed. In the dog, they have also shown, using cerebrospinal fluid, that endorphins are central neuromodulators of respiratory activity and that a dose-response relationship exists between endorphin level and the ventilatory effect independent of sleep state.

One recommendation for infants at risk for SIDS is to prescribe for them an apnea monitor which sounds an alarm when respiratory pauses and/or bradycardia (slow heart beat) extend beyond an acceptable limit. With Institute support, Dr. Willis J. Tompkins and staff at the University of Wisconsin, Madison, are developing a microprocessor-based neonatal apnea monitor. They have developed the initial hardware and software for a compact, multimicrocomputer-based neonatal apnea monitor for use in the neonatal intensive care unit. It is being modified for a minimal-hardware system to become a home monitor. In addition to the sounding of an alarm, the conditions that lead to it are displayed indicating seconds of unacceptable heart rate, rate at last accepted breath, seconds with no acceptable breaths, and the breath-hight threshold. The monitor needs to be clinically validated by comparing its alarm generation with events recorded in the clinical setting and must be further refined to reduce the false positive rate without losing high specificity for apnea detection. Even after this, it will be necessary to define more precisely infants at risk for SIDS.

Infectious Disease Processes and Immunology

It is not clear how the presence of infection and/or the infant's immunologic state may relate to the sudden infant death syndrome. It has been observed and documented that the infants who had recent upper respiratory infections are at greater risk. Among SIDS victims reports have appeared indicating that many had either a slight cold or stuffy nose of such a minor degree that medical advice was not sought. It is quite possible that the infection may act locally, probably in the respiratory tract.

Several grantees are examining the possible relationship to SIDS of intestinal infection and toxin produced by Clostridium botulinum. Dr. James Chin and staff at the Department of Health Services, California are studying Clostridial toxins as causes of SIDS. The first step in that research was just completed successfully with the development of a reliable test to detect the appearance of antibodies in patients hospitalized with infant botulism.

At Johns Hopkins Hospital, Dr. John G. Bartlett and associates are examining the intestinal contents of SIDS victims for Clostridium difficile and its toxin and found a positive culture in

27 percent of 58 victims of SIDS. They are looking for other viruses as well, such as rotavirus and coxsackie.

Grantee, Dr. Scott B. Halstead at the University of Hawaii, Honolulu, identified a model system in mice with dengue virus infection which progresses through a peripheral replication phase but is eliminated without causing mortality. This provides the opportunity to study viral immunological interactions and the examination of cell-mediated immune responses to virus infections. Simultaneously, Dr. Halstead is evaluating the role of immunological responses in Respiratory Syncytial Virus (RSV) infections in monkeys in order to determine the role of passively administered antibody during RSV infections. Some of these studies mimic the human infection, thus making it possible to study the interaction of antibody and immunocompetent cells in the respiratory tract during acute viral infections.

Major Research Program

During FY 1982, the Institute continued to support a large multidisciplinary SIDS project at the University of Maryland under the direction of Dr. Alfred Steinschneider. Risk profile scores were obtained in a prospective fashion on a large number of infants over a four-year period. In addition to newborn evaluations, these included data acquired from a large number of women through pregnancy, labor, delivery, and the postpartum period. These measures of risk encompass mathematical expressions of respiratory performance during sleep and feeding, and epidemiologic factors regarding recognized risk factors for SIDS (e.g., sibling death from SIDS, maternal drug dependence). Analysis of data began in FY 1982.

Nine infants studied physiologically within their first week of life died subsequently of SIDS. Compared to the normal parameters obtained in the study of more than 2,500 subjects, all SIDS victims had elevated apnea scores during either sleep or feeding. These findings are consistent with the hypothesis implicating both sleep apnea and laryngeal induced apnea in the etiology of SIDS.

Infants who tested high on the risk score during their first week of life were sent home with an apnea monitor. Of these 77 infants, 67 percent had at least one prolonged sleep apneic episode and 30 percent had documented episodes of bradycardia without concurrent prolonged apnea. These findings tend to support the hypothesis that newborns who develop prolonged apnea or bradycardia are physiologically different than the general population and, in a manner, similar to those infants who die of SIDS.

Other concurrent studies are examining the placentas of SIDS victims. Although tissue and other studies of the placentas have not shown differences between SIDS cases and birth-date matched controls, a reduction was found in the ratio of fetal weight over placental weight in SIDS victims.

The findings of subtle differences between SIDS victims and normal age-matched controls are helping not only in delineating the causes, but will also provide direction for studies aimed at developing a clinically useful approach for the early identification of infants at increased risk for SIDS.

NICHD Cooperative Epidemiologic Study of SIDS Risk Factors

The NICHD, through six data collection centers, identified more than 800 SIDS cases with 2 living controls for each case over a 15 month period. One control was matched for age only and the other for age, birthweight, and race. Postmortem tissue specimens and medical examiner records were obtained for the SIDS cases. Data also were collected on SIDS and control infants during a home interview and from prenatal, delivery, and postnatal medical records. Using the first 400 singleton SIDS infants and their controls, a preliminary analysis of risk factors has been performed. While few differences were identified between cases and controls for prenatal factors, SIDS infants as a group were more likely to have required postneonatal hospitalization and to have had signs and symptoms requiring medical treatment. Preterm delivery, low birthweight, low socioeconomic status, black race, maternal smoking during pregnancy, and young maternal age are indicative of increased risk for SIDS. So far in this study, clinically diagnosed apnea has not been identified as an important risk factor for SIDS. Effects of interactions of these factors on SIDS risk are being assessed. Additional multivariate analyses of these preliminary results and validation using the balance of the data set are ongoing.

National Heart, Lung, and Blood Institute

Topic areas for the research included control of breathing in respiratory failure, and maturational changes in the developing heart which suggest that the interplay of factors responsible for initiating and maintaining fibrillation (irregular contractions of the heart) may have a role in the etiology of the sudden infant death syndrome. Other studies are concerned with mediated respiratory responses to carbon dioxide, expiratory muscle function, and the role of the cerebellum in its control.

National Institute of Neurological and Communicative Disorders and Stroke

It has been suggested that central nervous system (CNS) dysfunction, particularly of the brainstem, may be implicated in SIDS. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) supports a number of research grants on the basic mechanisms of CNS dysfunction, some of which relate directly to SIDS. Some of these studies have as their focus the functional development of neural networks and the identification of developmental neuropathology. One study concerns the relationship of the maturation of the neurotransmitter systems to behavioral arousal. Another investigation is exploring the relationship of naturally occurring neuron death to the normal development of the mammalian central nervous system. The neural plasticity (the ability of early embryonic cells to alter in conformity with immediate environment) of the developing brain and the deficits in cell communication following perinatal hypoxia are under study in animals. Research is also being conducted on the concentrations of neuropeptides in autopsied human brains at different stages of development from the 20th week of fetal life through childhood. In these studies, neuropeptide concentrations in brain tissue from normal children are being compared to concentrations in children with neurological disorders. These investigations have the potential for providing the basic knowledge scientists need to better understand the neuropathology of SIDS.

THE SUDDEN INFANT DEATH SYNDROME
Obligations

	1980	1981	1982	1983 Estimate	198- Estimate
Public Health Service:					
National Institutes of Health:					
National Institute of Child Health and Human Development	$16,896,000	$18,766,000	$16,465,000	$18,400,000	$18,700,000
National Institute of Neurological & Communicative Disorders and Stroke	617,000	672,000	824,000	900,000	950,000
National Heart, Lung, and Blood Institute	268,000	250,000	250,000	250,000	250,000
Total, NIH	17,781,000	19,688,000	17,539,000	19,550,000	19,900,000
Health Resources and Services Administration:					
Bureau of Health Care Delivery and Assistance	20,802,000	20,780,000	--- 1/	--- 1/	--- 1/
TOTAL, PHS	38,583,000	40,468,000	17,539,000	19,550,000	19,900,000

1/ Funds included in the consolidated Maternal and Child Health Services Block Grant